

## Engineering a BCR-ABL-activated caspase for the selective elimination of leukemic cells.

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### Public Summary:

Increased understanding of the precise molecular mechanisms involved in cell survival and cell death signaling pathways offers the promise of harnessing these molecules to eliminate cancer cells without damaging normal cells. Tyrosine kinase oncoproteins promote the genesis of leukemias through both increased cell proliferation and inhibition of apoptotic cell death. Although tyrosine kinase inhibitors, such as the BCR-ABL inhibitor imatinib, have demonstrated remarkable efficacy in the clinic, drug-resistant leukemias emerge in some patients because of either the acquisition of point mutations or amplification of the tyrosine kinase, resulting in a poor long-term prognosis. Here, we exploit the molecular mechanisms of caspase activation and tyrosine kinase/adaptor protein signaling to forge a unique approach for selectively killing leukemic cells through the forcible induction of apoptosis. We have engineered caspase variants that can directly be activated in response to BCR-ABL. Because we harness, rather than inhibit, the activity of leukemogenic kinases to kill transformed cells, this approach selectively eliminates leukemic cells regardless of drug-resistant mutations.

### Scientific Abstract:

Increased understanding of the precise molecular mechanisms involved in cell survival and cell death signaling pathways offers the promise of harnessing these molecules to eliminate cancer cells without damaging normal cells. Tyrosine kinase oncoproteins promote the genesis of leukemias through both increased cell proliferation and inhibition of apoptotic cell death. Although tyrosine kinase inhibitors, such as the BCR-ABL inhibitor imatinib, have demonstrated remarkable efficacy in the clinic, drug-resistant leukemias emerge in some patients because of either the acquisition of point mutations or amplification of the tyrosine kinase, resulting in a poor long-term prognosis. Here, we exploit the molecular mechanisms of caspase activation and tyrosine kinase/adaptor protein signaling to forge a unique approach for selectively killing leukemic cells through the forcible induction of apoptosis. We have engineered caspase variants that can directly be activated in response to BCR-ABL. Because we harness, rather than inhibit, the activity of leukemogenic kinases to kill transformed cells, this approach selectively eliminates leukemic cells regardless of drug-resistant mutations.

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